UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/019,341	05/03/2002	Michael R. Hayden	SMAR-0013	8795

7590 11/19/2004

Jeffrey J King
Woodcock Washburn
46th Floor
One Liberty Place
Philadelphia, PA 19103

EXAMINER	
DUNSTON, JENNIFER ANN	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 11/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/019,341	HAYDEN ET AL.	
	Examiner	Art Unit	
	Jennifer Dunston	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *35-57* is/are pending in the application.

4a) Of the above claim(s) *37 and 52-57* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35,36 and 38-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/30/2002*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Sequence Alignment*.

DETAILED ACTION

Receipt is acknowledged of a preliminary amendment, filed 12/21/2001, in which claims 1-34 were cancelled and claims 35-57 were added. Receipt is also acknowledged of an amendment, filed 9/23/2004, in which claims 35, 36, 38 and 42 were amended and claims 52-57 were withdrawn.

Election/Restrictions

Applicant's election with traverse of Group II (claims 35-41 and 43-51) in the reply filed on 9/23/2004 is acknowledged. Further, it is acknowledged that claim 42 was amended to conform to the restriction requirement. Thus, Group II comprises claims 35-51. Regarding the further restriction of claims 36 and 37, Applicant's election with traverse of hyperlipidemia as the elected disease is acknowledged. The traversal is on the ground(s) that it would not present an undue burden on the Office to search all of the previously presented claims and all diseases because the diseases have a shared etiological component of LPL deficiency. This is not found persuasive because the Groups and diseases lack unity of invention. The shared special technical feature that unites the groups is the treatment of an LPL-responsive disease comprising administering an LPL S447X therapeutic, which is disclosed by Hayden et al (WO/9611276). Thus, the restriction requirement is deemed proper.

Further, searching the inventions of Groups I-III together would impose a serious search burden because they do not have a shared special technical feature that is a contribution over the prior art. Moreover, in the instant case, the search of the patent and non-patent literature for the methods of Groups I and II and the product of Group III are not coextensive. The methods of

Groups I and II comprise different method steps and thus require different searches of the patent and non-patent literature. The different diseases require separate searches in that they have distinct etiology and contributing environmental or genetic factors, which would dictate unique method steps not comprised in the method of treating hyperlipidemia. Further, a search for the composition of Group III will not necessarily identify the methods of Groups I or II.

The requirement is still deemed proper and is therefore made FINAL.

Claims 37, 52-57 are withdrawn from further consideration, as being drawn to a nonelected invention. An examination on the merits of claims 35, 36 and 38-51 follows.

Information Disclosure Statement

Receipt of an information disclosure statement, filed on 9/30/2002, is acknowledged. The signed and initialed PTO 1449 has been mailed with this action. Non-initialed references were not considered because the references were large volumes of work and relevant page numbers within the publication were not provided (see 37 CFR § 1.98(b)).

Sequence Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below.

Figures 1-4 of the instant specification contain protein and nucleic acid sequences. The sequence identifiers for the sequences are provided in the figure legends. Figure 1 is correctly

identified as SEQ ID NO: 1. Figure 2 is incorrectly identified as SEQ ID NO: 2. Figure 2 appears to contain the sequence of SEQ ID NO: 3. Figure 3 is incorrectly identified as SEQ ID NO: 3. Figure 3 appears to contain the sequence of SEQ ID NO: 2. Figure 4 contains a nucleic acid sequence of 3549 nucleotides and is identified as SEQ ID NO: 4. However, the nucleic acid sequence provided in the sequence listing for SEQ ID NO: 4 is only 2562 nucleotides long. Further, the figure legend for Figure 4 states that the figure "reproduces information available from Genbank Accession NM_000237 for a *Homo sapiens* lipoprotein lipase (LPL) mRNA." After performing a sequence search of SEQ ID NO: 4 against the commercial nucleic acid databases, SEQ ID NO: 4 failed to align with any known LPL sequences, including NM_000237. Therefore, the sequence provided in Figure 4 does not appear to be included in the paper copy or CRF of the sequence listing.

Further, lines 25 and 27 on page 20 of the specification contain nucleic acid sequences that are not identified by SEQ ID NOS.

In response to this office action, Applicant must comply with the sequence rules, 37 CFR 1.821 - 1.825. The nature of the non-compliance did not preclude an examination of the elected invention on the merits, the results of which are presented below.

Specification

The disclosure is objected to because of the following informalities: the specification does not provide antecedent basis for the phrase "hybridizes under stringent conditions," which is recited in claim 41. It is noted that claim 16 of the originally filed claims contains this phrase.

Appropriate correction is required.

Claim Objections

Claims 40, 43, 45 and 46 are objected to because of the following informalities: (i) claims 40 and 46 contain a hyphen in line 2 that should be deleted, and (ii) claims 43 and 45 contain a space within the term "S447X". Appropriate correction is required for all occurrences.

Claim 35 is objected to because of the following informalities: the claim recites the abbreviation "LPL". The abbreviation should be spelled out in the first appearance of the claims and should be followed by the abbreviation in parentheses. Appropriate correction is required.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 35, 36, 38, 39, 42-44, 47, 48 and 51 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 6,814,962 (hereafter '962) in view of Kozaki et al (Journal of Lipid Research, Vol. 34, pages 1765-1772, 1993; see the entire reference) as evidenced by Gotoda et al (Nucleic Acids Research, Vol. 17, No. 6, page 2351, 1989; see the entire reference).

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claims.

In the instant case, claims 1-6 of the '962 patent recite methods of treating dyslipoproteinaemia, hypertriglyceridaemia, hypercholesterolaemia, hyperlipidaemia, familial hypertriglyceridaemia, and combined familial hyperlipidaemia and postprandial hyperlipidaemia comprising administering to the patient a defective recombinant adenovirus comprising a nucleic acid sequence coding for a biologically active human lipoprotein lipase (LPL). The claims of the '962 patent differ from claims 35, 36, 38, 39, 42-44, 47, 48 and 51 of the instant application in that they fail to disclose the use of a nucleic acid sequence encoding the S447X variant of human LPL.

Kozaki et al teach an expression vector comprising the S447X LPL cDNA sequence (e.g. Figure 2). Further, Kozaki et al demonstrate that the S447X LPL protein has a specific activity about twice as high as wild type LPL (e.g. Figures 3 and 4, LPL-446).

The S447X LPL nucleic acid taught by Kozaki et al necessarily encodes an LPL S447X protein with at least 90% identity to SEQ ID NO: 3 and at least 95% identity to SEQ ID NO: 1. Kozaki et al disclose the primer sequences used to make the S447X truncation in the Figure 2 legend and cite Gotoda et al (Nucleic Acids Research, Vol. 17, No. 6, page 2351, 1989) as the source of the human sequence (e.g. page 1766, Site-directed mutagenesis, see cited reference 22). As demonstrated in the enclosed alignment, the nucleic acid sequence disclosed by Gotoda et al is 100% identical to SEQ ID NO: 3. Because SEQ ID NO: 1 has a c-terminal truncation of

2 amino acids relative to SEQ ID NO: 3, the nucleic acid sequence disclosed by Gotoda et al is capable of producing an alignment with 100% identity over the entire length of SEQ ID NO: 1.

Therefore, it would have been obvious to modify the method of claims 1-6 of the '962 patent to include the S447X nucleic acid sequence taught by Kozaki et al because the claims recite the use of a nucleic acid encoding a biologically active human LPL and Kozaki et al teach that the S447X truncation is a functional LPL protein. One would have been motivated to make such a modification in order to receive the expected benefit of increased LPL activity as taught by Kozaki et al.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 41 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 41 is vague and indefinite in that the metes and bounds of the phrase "hybridizes under stringent conditions" are unclear. The phrase is unclear in that there is no clear art-recognized definition for the term stringent and the specification fails to set forth a clear definition.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 40, 41, 45, 46, 49 and 50 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: The claims are drawn to a method for treating an LPL-responsive disease in a subject, comprising the administration of an LPL S447X therapeutic, which is a nucleic acid comprising a sequence encoding an RNA having at least 90% sequence identity to nucleotides 256-1599 of SEQ ID NO: 4 or that hybridizes to nucleotides 256-1599 of SEQ ID NO: 4. The invention is complex in that the nucleic acid sequence must code for a protein that is capable of functioning as a lipoprotein lipase (LPL) in the subject in an amount and duration sufficient to treat a disease.

Breadth of the claims: Regarding the nucleotide sequence, the claims are drawn narrowly to nucleotides 256-1599 of SEQ ID NO: 4.

Guidance of the specification and existence of working examples: The present specification does not provide guidance to support the claimed invention for gene therapy applications using any sequence with at least 90% identity to nucleotides 256-1599 of SEQ ID

NO: 4. Further, the specification does not provide a clear definition of stringent hybridization or any examples of stringent conditions and thus does not provide guidance for the use of those sequences for gene therapy applications. The specification asserts that SEQ ID NO: 4 encodes human lipoprotein lipase (e.g. paragraph bridging pages 5 and 6). However, in a search of the commercial nucleic acid databases nucleotides 256-1599 of SEQ ID NO: 4 failed to align with any known LPL sequences (e.g. the best local alignment had 9.6% identity). The specification does not disclose the identity of SEQ ID NO: 4 and does not provide evidence that SEQ ID NO: 4 encodes a protein that is capable of functioning as an LPL S447X therapeutic.

State of the art and predictability of the art: An analysis of the prior art as of the effective filing date of the present application shows the successful delivery of human LPL cDNA to mice *in vivo* using adenoviral-mediated gene transfer (Excoffon et al, Arteriosclerosis, Thrombosis, and Vascular Biology, Vol. 17, No. 11, pages 2532-2539, 1997; e.g. Abstract; Kobayashi et al. The Journal of Biological Chemistry, Vol. 271, No. 42, pages 26296-26301, 1996; e.g. page 26297, *Study Animals*; Table I). The expression of LPL in LPL-deficient mice resulted in reduced triglyceride levels (e.g. Excoffon et al, page 2535, right column). Further, the LPL sequence has been highly conserved across evolution. Kirchgessner et al reported a 94% amino acid identity and 98% similarity between mouse and human lipoprotein lipase sequences (The Journal of Biological Chemistry, Vol. 262, No. 18, pages 8463-8466, 1987; e.g. Figure 2; paragraph bridging pages 8464-8465). Due to the low percent identity (<10%) of nucleotides 256-1599 of SEQ ID NO: 4 to known sequences, it seems unlikely that the nucleotide sequence provided in the instant specification encodes a lipoprotein lipase. Therefore, without any

evidence that the nucleotide sequence codes for a functional LPL protein, it would be highly unpredictable to practice the claimed invention.

Amount of experimentation necessary: The quantity of experimentation necessary to carry out the claimed invention is high as the skilled artisan could not rely on the prior art or the present specification to teach how to use the claimed methods. In order to determine how to use the method to treat a condition, one of skill in the art would have to determine if nucleotides 256-1599 pf SEQ ID NO: 4 contain an open reading frame (ORF), what the function of the ORF, and whether the ORF is capable of functioning as a therapeutic LPL S447X protein. One would have to determine the effect exogenous expression would have in any cell type, whether the effect could be exploited for treatment of a disease, how to deliver the given nucleic acid to the appropriate target cells with specificity and efficiency, and how to get sufficient expression to induce at least some therapeutic effect. Since neither the prior art nor the specification provides the answers to all of these questions, it would require a large quantity of trial and error experimentation by the skilled artisan to do so.

Based on the unknown identity of SEQ ID NO: 4, the unpredictability in the area of the invention, the lack of sufficient guidance or working examples in the specification and the quantity of experimentation necessary, it would clearly require undue experimentation by one of skill in the art to determine how to make and/or use the claimed invention.

Claims 35, 36, 38, 39, 42-44, 47, 48 and 51 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating hyperlipidemia associated with LPL or ApoE deficiency, comprising the administration of an

adenoviral vector containing the coding sequence for an LPL S447X protein, does not reasonably provide enablement for the treatment of any other conditions. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention and breadth of the claims: The claims are drawn to a method of treating an LPL-responsive disease in a subject, comprising administering to the subject an effective amount of a nucleic acid encoding an LPL S447X protein (i.e. gene therapy). The claims are broad in that they read on the treatment of any disease treatable by the *in vivo* production of LPL protein (i.e. an LPL-responsive disease). Claim 36 further limits the LPL-responsive disease to hyperlipidemia.

The nature of the invention is complex in that lipid metabolism is a highly complex process with multiple genetic and environmental modifiers contributing to the health of the individual.

Guidance of the specification and existence of working examples: The present specification provides little or no guidance to support the claimed invention for gene therapy applications other than for the reduction in triglyceride and cholesterol levels in LPL deficient heterozygotes and homozygotes, and ApoE deficient homozygotes. In addition to LPL and

ApoE deficiency, the specification provides a long list of putative LPL-responsive diseases (e.g. page 4, lines 2-15) but fails to demonstrate a therapeutic effect of LPL expression for any of the listed conditions in any model system. Although Applicant has demonstrated an increase in LPL activity subsequent to the administration of an adenovirus carrying the LPL S447X coding sequence, there is no support in the specification to indicate that an increase in LPL activity is sufficient to treat the disclosed LPL-responsive conditions.

The working examples disclose adenovirus-mediated gene transfer of the human LPL S447X coding sequence (i.e. Ad-447) to LPL +/-, LPL-/- and ApoE-/- mice (Examples 1, 2 and 5). The administration of Ad-447 to these mice resulted in a reduction of total and HDL cholesterol and triglyceride levels. Thus, these examples demonstrate that the expression of LPL results in a decrease in hyperlipidemia (hypercholesterolemia and hypertriglyceridemia) in mice with this specific genetic background.

Further, the working examples disclose a genetic association of the LPL S447X genotype with the New York Heart Association (NYHA) classification for prescription of activity for cardiac patients and with protection against coronary heart disease (Examples 3 and 4).

State of the art: An analysis of the prior art as of the effective filing date of the present application shows the complete lack of support for a broad class of diseases treatable by the administration of an LPL nucleic acid. Adenoviral-mediated gene transfer of the human LPL coding sequence was shown to result in decreased triglyceride levels in LPL -/-, ApoE -/-, LDL receptor (LDLr) and hepatic lipase (HL) -/- mice, decreased plasma cholesterol in ApoE-/-, LDLr -/-, and HL -/- mice, and decreased phospholipid concentrations in HL-/- mice (Excoffon et al, e.g. page 2535, right column; Kobayashi et al, e.g. Table II; Zsigmond et al, Human Gene

Therapy, Vol. 8, pages 1921-1933, 1997, e.g. Table 1). In a post filing review of the art, Mead et al acknowledge that LPL has been directly or directly implicated in several pathophysiological conditions that are characterized by marked hypertriglyceridemia, including chylomicronaemia, cachexia, insulin resistance and diabetes, obesity and atherosclerosis (Mead et al., J. Mol. Med., Vol. 80, pages 753-769, 2002; e.g. page 760, left column, paragraph 3). Regarding chylomicronaemia, Mead et al note that in addition to a deficiency in LPL, this condition can result from a deficiency of the LPL cofactor apoC2 (e.g. page 760, right column, paragraph 1). Thus, if an individual lacks the necessary cofactors for LPL function, then that individual cannot be treated for chylomicronaemia by increasing the level of LPL. Further, obesity and atherosclerosis are multifactorial diseases, in which the role of LPL is not clear (e.g. page 760-761, *Obesity* and *Atherosclerosis*). While this reference indicates the promise of gene therapy, it will require further research before becoming a reality (e.g. page 763, left column).

Regarding the use of genetic association to determine the therapeutic potential of a gene product, Page et al (Am. J. Hum. Genet. Vol. 73, pages 711-719, 2003) state that "there is no explicit consensus about what constitutes sufficient evidence to establish causation from association" (see the paragraph bridging pages 711-712). Further, Page et al note that a p-value of less than 0.05 is useful to reduce the rate of false positives, but it is only one component in a set of criteria for causation (see the paragraph bridging pages 713-714). Thus, a single experiment demonstrating an association does not prove causation or the ability to treat an individual with the associated gene product.

In a review on the current status of gene therapy, the continued, major obstacles to successful gene therapy are gene delivery and sustained expression of the gene. Regarding non-

viral methods for gene delivery, Verma et al indicates that most approaches suffer from poor efficiency and transient expression of the gene (p. 239, col. 3, 2nd paragraph). Likewise, Luo et al (Nature Biotechnology, Vol. 18, pages 33-37, 2000) indicates that non-viral synthetic delivery systems are very inefficient. See p. 33, Abstract and col. 1, 1st and 2nd paragraphs. While the two references indicate the promise of gene therapy, it is still a technique of the future and advancements in our understanding of the basics of gene delivery and expression must be made before gene therapy becomes a useful technique. See Verma et al, p. 242, col. 2-3; Luo et al, p. 33, col. 1, 1st paragraph.

Predictability of the art: The area of the invention is unpredictable. In 1999, the administration of an E1 and E4 deleted human adenovirus type 5 vector to an 18-year-old individual unexpectedly resulted in the death of the individual (Edelstein et al, The Journal of Gene Medicine, Vol. 6, pages 597-602; e.g. page 599, The hopes and the setbacks). Further, in 2000, the administration of a retrovirus vector resulted in two of ten children developing a leukemia-like condition from the integration of the vector near the LMO2 proto-oncogene promoter (e.g. page 599, The hopes and the setbacks). The skilled artisan at the time the present invention was made recognized the difficulty of achieving sufficient heterologous gene expression to induce any therapeutic effect.

Amount of experimentation necessary: The quantity of experimentation necessary to carry out the claimed invention is high as the skilled artisan could not rely on the prior art or the present specification to teach how to use the full scope of the claimed methods. In order to determine how to use the method to treat a condition, one of skill in the art would have to determine whether the effect of LPL expression could be exploited for treatment of a disease,

how to deliver the given nucleic acid to the appropriate target cells with specificity and efficiency, and how to get sufficient expression to induce at least some therapeutic effect. Since neither the prior art nor the specification provides the answers to all of these questions, it would require a large quantity of trial and error experimentation by the skilled artisan to do so.

Based on the broad scope of the claims, the unpredictability in the area of the invention, the lack of sufficient guidance or working examples in the specification and the quantity of experimentation necessary, it would clearly require undue experimentation by one of skill in the art to determine how to use the full scope of the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 35, 36, 38, 39, 42-44, 47, 48 and 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hayden et al (WO 96/11276; see the entire reference) in view of Kozaki et al (Journal of Lipid Research, Vol. 34, pages 1765-1772, 1993; see the entire reference) as evidenced by Gotoda et al (Nucleic Acids Research, Vol. 17, No. 6, page 2351, 1989; see the entire reference).

Hayden et al teach the *in vivo* transduction of human cells with viral gene therapy vectors comprising the full-length LPL cDNA sequence for the treatment of hypertriglyceridemia (i.e. one form of hyperlipidemia) resulting from LPL deficiency (e.g. page 11, lines 10-31; page 12, lines 1-31).

Hayden et al do not teach the administration of a S447X LPL cDNA sequence.

Kozaki et al teach an expression vector comprising the S447X LPL cDNA sequence (e.g. Figure 2). Further, Kozaki et al demonstrate that the S447X LPL protein has a specific activity about twice as high as wild type LPL (e.g. Figures 3 and 4, LPL-446). Moreover, Kozaki et al suggest that the S447X mutation may have some protective effect against the development of hypertriglyceridemia (e.g. page 1771, left column, paragraph 1).

The S447X LPL nucleic acid taught by Kozaki et al necessarily encodes an LPL S447X protein with at least 90% identity to SEQ ID NO: 3 and at least 95% identity to SEQ ID NO: 1. Kozaki et al disclose the primer sequences used to make the S447X truncation in the Figure 2 legend and cite Gotoda et al (Nucleic Acids Research, Vol. 17, No. 6, page 2351, 1989) as the source of the human sequence (e.g. page 1766, Site-directed mutagenesis, see cited reference 22). As demonstrated in the enclosed alignment, the nucleic acid sequence disclosed by Gotoda et al is 100% identical to SEQ ID NO: 3. Because SEQ ID NO: 1 has a c-terminal truncation of

2 amino acids relative to SEQ ID NO: 3, the nucleic acid sequence disclosed by Gotoda et al is capable of producing an alignment with 100% identity over the entire length of SEQ ID NO: 1.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the viral gene therapy vector of Hayden et al to include the S447X nucleic acid sequence taught by Kozaki et al in place of the wild type LPL sequence because Hayden et al teach it is within the ordinary skill in the art to use an LPL coding sequence in the viral gene therapy vector for the treatment of hyperlipidemia associated with LPL deficiency and Kozaki et al teach that the S447X truncation is a functional LPL protein.

One would have been motivated to make such a modification in order to receive the expected benefit of increased LPL activity and a protective effect against the development of hypertriglyceridemia as taught by Kozaki et al. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR, http://pair-direct.uspto.gov) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Jennifer Dunston
Examiner
Art Unit 1636

jad

TERRY MCKELVEY
PRIMARY EXAMINER

```
                     /mol_type="mRNA"
                     /db_xref="taxon:9606"
                     /chromosome="8p22"
                     /clone="HLC 601"
                     /cell_type="monocytic leukemia THP-1 cells"
     CDS             144. .1571
                     /note="unnamed protein product; precursor protein"
                     /codon_start=1
                     /protein_id="CAA38372.1"
                     /db_xref="GI:34383"
                     /db_xref="GOA:P06858"
                     /db_xref="Swiss-Prot:P06858"
                     /translation="MESKALLVLTLAVWLQSLTASRGGVAAADQRRDFIDIESKFALR
                     TPEDTAEDTCHLIPGVAESVATCHFNHSSKTFMVIHGWTVTGMYESWVPKLVAALYKR
                     EPDSNVIVVDWLSRAQEHYPVSAGYTKLVGQDVARFINWMEEEFNYPLDNVHLLGYSL
                     GAHAAGIAGSLTNKKVNRITGLDPAGPNFEYAEAPSRLSPDDADFVDVLHTFTRGSPG
                     RSIGIQKPVGHVDIYPNGGTFQPGCNIGEAIRVIAERGLGDVDQLVKCSHERSIHLFI
                     DSLLNEENPSKAYRCSSKEAFEKGLCLSCRKNRCNNLGYEINKVRAKRSSKMYLKTRS
                     QMPYKVFHYQVKIHFSGTESETHTNQAFEISLYGTVAESENIPFTLPEVSTNKTYSFL
                     IYTEVDIGELLMLKLKWKSDSYFSWSDWWSSPGFAIQKIRVKAGETQKKVIFCSREKV
                     SHLQKGKAPAVFVKCHDKSLNKKSG"
     sig_peptide     144. .224
                     /note="signal peptide"
     mat_peptide     225. .1568
                     /product="mature lipoprotein lipase"
ORIGIN

Alignment Scores:
Pred. No.:                2.97e-202     Length:          1612
Score:                    2385.00       Matches:         448
Percent Similarity:       100.00%       Conservative:    0
Best Local Similarity:    100.00%       Mismatches:      0
Query Match:              100.00%       Indels:          0
DB:                       9             Gaps:            0

US-10-019-341-3 (1-448) x HSLIPAS (1-1612)

Qy          1 AlaAspGlnArgArgAspPheIleAspIleGluSerLysPheAlaLeuArgThrProGlu 20
              |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        225 GCCGACCAAAGAAGAGATTTTATCGACATCGAAAGTAAATTTGCCCTAAGGACCCCTGAA 284

Qy         21 AspThrAlaGluAspThrCysHisLeuIleProGlyValAlaGluSerValAlaThrCys 40
              |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        285 GACACAGCTGAGGACACTTGCCACCTCATTCCCGGAGTAGCAGAGTCCGTGGCTACCTGT 344

Qy         41 HisPheAsnHisSerSerLysThrPheMetValIleHisGlyTrpThrValThrGlyMet 60
              |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        345 CATTTCAATCACAGCAGCAAAACCTTCATGGTGATCCATGGCTGGACGGTAACAGGAATG 404

Qy         61 TyrGluSerTrpValProLysLeuValAlaAlaLeuTyrLysArgGluProAspSerAsn 80
              |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        405 TATGAGAGTTGGGTGCCAAAACTTGTGGCCGCCCTGTACAAGAGAGAACCAGACTCCAAT 464

Qy         81 ValIleValValAspTrpLeuSerArgAlaGlnGluHisTyrProValSerAlaGlyTyr 100
              |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        465 GTCATTGTGGTGGACTGGCTGTCACGGGCTCAGGAGCATTACCCAGTGTCCGCGGGCTAC 524

Qy        101 ThrLysLeuValGlyGlnAspValAlaArgPheIleAsnTrpMetGluGluGluPheAsn 120
              |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        525 ACCAAACTGGTGGGACAGGATGTGGCCCGGTTTATCAACTGGATGGAGGAGGAGTTTAAC 584

Qy        121 TyrProLeuAspAsnValHisLeuLeuGlyTyrSerLeuGlyAlaHisAlaAlaGlyIle 140
              |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        585 TACCCTCTGGACAATGTCCATCTCTTGGGATACAGCCTTGGAGCCCATGCTGCTGGCATT 644

Qy        141 AlaGlySerLeuThrAsnLysLysValAsnArgIleThrGlyLeuAspProAlaGlyPro 160
              |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        645 GCAGGAAGTCTGACCAATAAGAAAGTCAACAGAATTACTGGCCTCGATCCAGCTGGACCT 704

Qy        161 AsnPheGluTyrAlaGluAlaProSerArgLeuSerProAspAspAlaAspPheValAsp 180
              |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        705 AACTTTGAGTATGCAGAAGCCCCGAGTCGTCTTTCTCCTGATGATGCAGATTTTGTAGAC 764

Qy        181 ValLeuHisThrPheThrArgGlySerProGlyArgSerIleGlyIleGlnLysProVal 200
              |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        765 GTCTTACACACATTCACCAGAGGGTCCCCTGGTCGAAGCATTGGAATCCAGAAACCAGTT 824

Qy        201 GlyHisValAspIleTyrProAsnGlyGlyThrPheGlnProGlyCysAsnIleGlyGlu 220
              |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        825 GGGCATGTTGACATTTACCCGAATGGAGGTACTTTTCAGCCAGGATGTAACATTGGAGAA 884

Qy        221 AlaIleArgValIleAlaGluArgGlyLeuGlyAspValAspGlnLeuValLysCysSer 240
              |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        885 GCTATCCGCGTGATTGCAGAGAGAGGACTTGGAGATGTGGACCAGCTAGTGAAGTGCTCC 944

Qy        241 HisGluArgSerIleHisLeuPheIleAspSerLeuLeuAsnGluGluAsnProSerLys 260
              |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        945 CACGAGCGCTCCATTCATCTCTTCATCGACTCTCTGTTGAATGAAGAAAATCCAAGTAAG 1004

Qy        261 AlaTyrArgCysSerSerLysGluAlaPheGluLysGlyLeuCysLeuSerCysArgLys 280
              |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1005 GCCTACAGGTGCAGTTCCAAGGAAGCCTTTGAGAAAGGGCTCTGCTTGAGTTGTAGAAAG 1064

Qy        281 AsnArgCysAsnAsnLeuGlyTyrGluIleAsnLysValArgAlaLysArgSerSerLys 300
              |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1065 AACCGCTGCAACAATCTGGGCTATGAGATCAATAAAGTCAGAGCCAAAAGAAGCAGCAAA 1124

Qy        301 MetTyrLeuLysThrArgSerGlnMetProTyrLysValPheHisTyrGlnValLysIle 320
              |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1125 ATGTACCTGAAGACTCGTTCTCAGATGCCCTACAAAGTCTTCCATTACCAAGTAAAGATT 1184

Qy        321 HisPheSerGlyThrGluSerGluThrHisThrAsnGlnAlaPheGluIleSerLeuTyr 340
              |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1185 CATTTTTCTGGGACTGAGAGTGAAACCCATACCAATCAGGCCTTTGAGATTTCTCTGTAT 1244

Qy        341 GlyThrValAlaGluSerGluAsnIleProPheThrLeuProGluValSerThrAsnLys 360
              |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1245 GGCACCGTGGCCGAGAGTGAGAACATCCCATTCACTCTGCCTGAAGTTTCCACAAATAAG 1304

Qy        361 ThrTyrSerPheLeuIleTyrThrGluValAspIleGlyGluLeuLeuMetLeuLysLeu 380
              |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1305 ACCTACTCCTTCCTAATTTACACAGAGGTAGATATTGGAGAACTACTCATGTTGAAGCTC 1364

Qy        381 LysTrpLysSerAspSerTyrPheSerTrpSerAspTrpTrpSerSerProGlyPheAla 400
              |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1365 AAATGGAAGAGTGATTCATACTTTAGCTGGTCAGACTGGTGGAGCAGTCCCGGCTTCGCC 1424

Qy        401 IleGlnLysIleArgValLysAlaGlyGluThrGlnLysLysValIlePheCysSerArg 420
              |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1425 ATTCAGAAGATCAGAGTAAAAGCAGGAGAGACTCAGAAAAAGGTGATCTTCTGTTCTAGG 1484

Qy        421 GluLysValSerHisLeuGlnLysGlyLysAlaProAlaValPheValLysCysHisAsp 440
              |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1485 GAGAAAGTGTCTCATTTGCAGAAAGGAAAGGCACCTGCGGTATTTGTGAAATGCCATGAC 1544

Qy        441 LysSerLeuAsnLysLysSerGly 448
              |||||||||||||||||||||||||
Db       1545 AAGTCTCTGAATAAGAAGTCAGGC 1568

RESULT 2
HSLPLR
LOCUS       HSLPLR                  1924 bp    mRNA    linear   PRI 22-MAR-1995
DEFINITION  Human mRNA for lipoprotein lipase (EC 3.1.1.34).
ACCESSION   X14390
VERSION     X14390.1  GI:34404
KEYWORDS    lipoprotein lipase.
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE   1  (bases 1 to 1924)
  AUTHORS   Gotoda,T., Senda,M., Gamou,T., Furuichi,Y. and Oka,K.
  TITLE     Nucleotide sequence of human cDNA coding for a lipoprotein lipase
            (LPL) cloned from placental cDNA library
  JOURNAL   Nucleic Acids Res. 17 (6), 2351 (1989)
  MEDLINE   89202044
```

```
   PUBMED   2701938
REFERENCE   2  (bases 1 to 1924)
  AUTHORS   Senda,M.
  TITLE     Direct Submission
  JOURNAL   Submitted (15-FEB-1989) Senda M., Department of Molecular Genetics,
            Nippon Roche Research Center, 200 Kaziwara Kamakura shi, Kanagawa
            247, Japan
COMMENT     The sequence overlaps with that reported by Wion et. al. in Science
            235:1638-1641(1987).
FEATURES             Location/Qualifiers
     source          1. .1924
                     /organism="Homo sapiens"
                     /mol_type="mRNA"
                     /db_xref="taxon:9606"
                     /map="chromosome 8p22"
                     /tissue_type="placenta"
                     /clone_lib="placenta cDNA"
     CDS             118. .1545
                     /note="unnamed protein product; lipase precurser (AA -27
                     to 448)"
                     /codon_start=1
                     /protein_id="CAA32564.1"
                     /db_xref="GI:34405"
                     /db_xref="GOA:P06858"
                     /db_xref="Swiss-Prot:P06858"
                     /translation="MESKALLVLTLAVWLQSLTASRGGVAAADQRRDFIDIESKFALR
                     TPEDTAEDTCHLIPGVAESVATCHFNHSSKTFMVIHGWTVTGMYESWVPKLVAALYKR
                     EPDSNVIVVDWLSRAQEHYPVSAGYTKLVGQDVARFINWMEEEFNYPLDNVHLLGYSL
                     GAHAAGIAGSLTNKKVNRITGLDPAGPNFEYAEAPSRLSPDDADFVDVLHTFTRGSPG
                     RSIGIQKPVGHVDIYPNGGTFQPGCNIGEAIRVIAERGLGDVDQLVKCSHERSIHLFI
                     DSLLNEENPSKAYRCSSKEAFEKGLCLSCRKNRCNNLGYEINKVRAKRSSKMYLKTRS
                     QMPYKVFHYQVKIHFSGTESETHTNQAFEISLYGTVAESENIPFTLPEVSTNKTYSFL
                     IYTEVDIGELLMLKLKWKSDSYFSWSDWWSSPGFAIQKIRVKAGETQKKVIFCSREKV
                     SHLQKGKAPAVFVKCHDKSLNKKSG"
     sig_peptide     118. .198
                     /note="signal peptide (AA -27 to -1)"
     mat_peptide     199. .1542
                     /product="mature lipase (AA 1-448)"
ORIGIN

Alignment Scores:
Pred. No.:              3.76e-202       Length:         1924
Score:                  2385.00         Matches:        448
Percent Similarity:     100.00%         Conservative:   0
Best Local Similarity:  100.00%         Mismatches:     0
Query Match:            100.00%         Indels:         0
DB:                     9               Gaps:           0

US-10-019-341-3 (1-448) x HSLPLR (1-1924)

Qy          1 AlaAspGlnArgArgAspPheIleAspIleGluSerLysPheAlaLeuArgThrProGlu 20
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        199 GCCGACCAAAGAAGAGATTTTATCGACATCGAAAGTAAATTTGCCCTAAGGACCCCTGAA 258

Qy         21 AspThrAlaGluAspThrCysHisLeuIleProGlyValAlaGluSerValAlaThrCys 40
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        259 GACACAGCTGAGGACACTTGCCACCTCATTCCCGGAGTAGCAGAGTCCGTGGCTACCTGT 318

Qy         41 HisPheAsnHisSerSerLysThrPheMetValIleHisGlyTrpThrValThrGlyMet 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        319 CATTTCAATCACAGCAGCAAAACCTTCATGGTGATCCATGGCTGGACGGTAACAGGAATG 378

Qy         61 TyrGluSerTrpValProLysLeuValAlaAlaLeuTyrLysArgGluProAspSerAsn 80
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        379 TATGAGAGTTGGGTGCCAAAACTTGTGGCCGCCCTGTACAAGAGAGAACCAGACTCCAAT 438

Qy         81 ValIleValValAspTrpLeuSerArgAlaGlnGluHisTyrProValSerAlaGlyTyr 100
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        439 GTCATTGTGGTGGACTGGCTGTCACGGGCTCAGGAGCATTACCCAGTGTCCGCGGGCTAC 498

Qy        101 ThrLysLeuValGlyGlnAspValAlaArgPheIleAsnTrpMetGluGluGluPheAsn 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        499 ACCAAACTGGTGGGACAGGATGTGGCCCGGTTTATCAACTGGATGGAGGAGGAGTTTAAC 558

Qy        121 TyrProLeuAspAsnValHisLeuLeuGlyTyrSerLeuGlyAlaHisAlaAlaGlyIle 140
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        559 TACCCTCTGGACAATGTCCATCTCTTGGGATACAGCCTTGGAGCCCATGCTGCTGGCATT 618

Qy        141 AlaGlySerLeuThrAsnLysLysValAsnArgIleThrGlyLeuAspProAlaGlyPro 160
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        619 GCAGGAAGTCTGACCAATAAGAAAGTCAACAGAATTACTGGCCTCGATCCAGCTGGACCT 678

Qy        161 AsnPheGluTyrAlaGluAlaProSerArgLeuSerProAspAspAlaAspPheValAsp 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        679 AACTTTGAGTATGCAGAAGCCCCGAGTCGTCTTTCTCCTGATGATGCAGATTTTGTAGAC 738

Qy        181 ValLeuHisThrPheThrArgGlySerProGlyArgSerIleGlyIleGlnLysProVal 200
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        739 GTCTTACACACATTCACCAGAGGGTCCCCTGGTCGAAGCATTGGAATCCAGAAACCAGTT 798

Qy        201 GlyHisValAspIleTyrProAsnGlyGlyThrPheGlnProGlyCysAsnIleGlyGlu 220
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        799 GGGCATGTTGACATTTACCCGAATGGAGGTACTTTTCAGCCAGGATGTAACATTGGAGAA 858

Qy        221 AlaIleArgValIleAlaGluArgGlyLeuGlyAspValAspGlnLeuValLysCysSer 240
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        859 GCTATCCGCGTGATTGCAGAGAGAGGACTTGGAGATGTGGACCAGCTAGTGAAGTGCTCC 918

Qy        241 HisGluArgSerIleHisLeuPheIleAspSerLeuLeuAsnGluGluAsnProSerLys 260
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        919 CACGAGCGCTCCATTCATCTCTTCATCGACTCTCTGTTGAATGAAGAAAATCCAAGTAAG 978

Qy        261 AlaTyrArgCysSerSerLysGluAlaPheGluLysGlyLeuCysLeuSerCysArgLys 280
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        979 GCCTACAGGTGCAGTTCCAAGGAAGCCTTTGAGAAAGGGCTCTGCTTGAGTTGTAGAAAG 1038

Qy        281 AsnArgCysAsnAsnLeuGlyTyrGluIleAsnLysValArgAlaLysArgSerSerLys 300
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1039 AACCGCTGCAACAATCTGGGCTATGAGATCAATAAAGTCAGAGCCAAAAGAAGCAGCAAA 1098

Qy        301 MetTyrLeuLysThrArgSerGlnMetProTyrLysValPheHisTyrGlnValLysIle 320
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1099 ATGTACCTGAAGACTCGTTCTCAGATGCCCTACAAAGTCTTCCATTACCAAGTAAAGATT 1158

Qy        321 HisPheSerGlyThrGluSerGluThrHisThrAsnGlnAlaPheGluIleSerLeuTyr 340
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1159 CATTTTTCTGGGACTGAGAGTGAAACCCATACCAATCAGGCCTTTGAGATTTCTCTGTAT 1218

Qy        341 GlyThrValAlaGluSerGluAsnIleProPheThrLeuProGluValSerThrAsnLys 360
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1219 GGCACCGTGGCCGAGAGTGAGAACATCCCATTCACTCTGCCTGAAGTTTCCACAAATAAG 1278

Qy        361 ThrTyrSerPheLeuIleTyrThrGluValAspIleGlyGluLeuLeuMetLeuLysLeu 380
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1279 ACCTACTCCTTCCTAATTTACACAGAGGTAGATATTGGAGAACTACTCATGTTGAAGCTC 1338

Qy        381 LysTrpLysSerAspSerTyrPheSerTrpSerAspTrpTrpSerSerProGlyPheAla 400
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1339 AAATGGAAGAGTGATTCATACTTTAGCTGGTCAGACTGGTGGAGCAGTCCCGGCTTCGCC 1398

Qy        401 IleGlnLysIleArgValLysAlaGlyGluThrGlnLysLysValIlePheCysSerArg 420
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1399 ATTCAGAAGATCAGAGTAAAAGCAGGAGAGACTCAGAAAAAGGTGATCTTCTGTTCTAGG 1458

Qy        421 GluLysValSerHisLeuGlnLysGlyLysAlaProAlaValPheValLysCysHisAsp 440
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1459 GAGAAAGTGTCTCATTTGCAGAAAGGAAAGGCACCTGCGGTATTTGTGAAATGCCATGAC 1518

Qy        441 LysSerLeuAsnLysLysSerGly 448
              |||||||||||||||||||||||||
Db       1519 AAGTCTCTGAATAAGAAGTCAGGC 1542
```

RESULT 3
AK092286
LOCUS AK092286 2385 bp mRNA linear PRI 30-JAN-2004
DEFINITION Homo sapiens cDNA FLJ34967 fis, clone NTONG2004690, highly similar